PROPHYLACTIC PREGABALIN TO DECREASE PAIN DURING MEDICAL ABORTION: A RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

OBJECTIVE: To evaluate whether prophylactic pregabalin reduces the level of maximum pain experienced with mifepristone-misoprostol medical abortion.

METHODS: We conducted a randomized, double-blind, placebo-controlled clinical trial of women initiating a medical abortion up to 70 days of gestation. After taking mifepristone, participants were randomized to a capsule of pregabalin 300 mg or a matched placebo to be taken at the time of buccal misoprostol. All participants were dispensed ibuprofen and oxycodone with acetaminophen as additional analgesia to be taken as needed. Electronic surveys were sent via text message link at six time points over 72 hours to assess the primary outcome of maximum pain, as well as secondary outcomes such as analgesic use and adverse effects.

RESULTS: From June 2015 to October 2016, 110 women were randomized to receive 300 mg of pregabalin or a matched placebo. Demographic characteristics were similar between groups. The primary outcome of maximum pain score in the pregabalin group was 5.0 versus 5.5 in the placebo group (standard deviations 2.6 and 2.2, respectively; p=0.32). More participants in the pregabalin group did not need additional analgesia. No ibuprofen was taken by 27% of the pregabalin group versus 12% placebo (p=0.04). No oxycodone with acetaminophen was taken by 69% of the pregabalin group versus 50% placebo (p=0.04). Satisfaction scores for the abortion process were highest in the pregabalin group (very satisfied: 41% versus 22%; p=0.03), as were satisfaction scores for the analgesic regimen (very satisfied: 47% versus 22%; p=0.006).

CONCLUSION: Maximum pain scores were not significantly different between the pregabalin and placebo groups, though women who received pregabalin were less likely to require any

ibuprofen or oxycodone with acetaminophen, and were more likely to report higher satisfaction scores.

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CHAPTER 1: INTRODUCTION

Medical abortion with mifepristone and misoprostol has been increasing in frequency, even as total abortion rates have decreased, with approximately 272,400 medical abortions performed in the United States in 2014. Between 2011 and 2014, the total abortion rate in the United States declined 12%, while early medical abortions increased from 24 to 31% of all nonhospital abortions.[1] Providing adequate analgesia at the time of medical abortion is an important reproductive health issue.

Women undergoing a medical abortion with mifepristone and misoprostol consistently report moderate to severe pain, with maximum pain scores ranging from seven to eight on an 11-point scale.[2-4] Pain has also been reported to last five or more days for a majority of women.[2] Limited data exists regarding the most effective analgesic regimen, though ibuprofen has been found to be superior to acetaminophen and is commonly prescribed.[4] There has been no difference found between prophylactic or therapeutic use of ibuprofen in reduction of medical abortion pain.[2] A review of pain management during medical abortion revealed that 75% of women also require a narcotic to manage their pain.[5] With nationwide goals of reducing narcotic use, finding a non-narcotic replacement for analgesia would be ideal.

Medical abortion is associated with multiple side effects, particularly after misoprostol administration. The most common side effects reported after buccal misoprostol include nausea (34-75%), vomiting (16-47%), diarrhea (2-61%), weakness (21-58%), headache (2-44%), fever (4-48%), and dizziness (12-41%).[6] The ideal analgesic regimen would decrease pain while not adding any significant side effects.

Pregabalin is a gamma-aminobutyric acid (GABA) analog with acute analgesic effects. It has 90% bioavailability, reaches its maximum therapeutic effect in less than one hour, and has a half-life of 5.5 to 6.7 hours.[7] This rapid onset of action could be ideal for co-administration with misoprostol, as it would reach its peak effect at the same time as the misoprostol dissolves buccally. Co-administration would also simplify the process for patients, instead of having to remember to take multiple pills at specific times.

Pregabalin is increasingly used as a preoperative medication to decrease acute pain. A meta-analysis of perioperative pregabalin in 55 trials of different surgical procedures showed a significant reduction in pain scores and opioid use compared to placebo. This analysis included a wide range of surgical procedures, including laparoscopic cholecystectomy, arthroscopy, spinal surgery, and abdominal hysterectomy. There was no significant difference between single preoperative dosing and repeated dosing, though increased sedation was seen with multiple doses of 300 mg capsules.[8] Another meta-analysis specifically of gynecologic procedures demonstrated decreased pain scores, decreased total analgesic use, and decreased opioid use with preoperative pregabalin, with no difference in adverse effects compared with placebo.[9]

The most commonly reported side effects of pregabalin are dizziness (31% pregabalin, 9% placebo) and somnolence (22% pregabalin, 7% placebo).[7,10] Other side effects include blurred vision, dry mouth, increased appetite, and constipation.[7] In addition to decreasing pain scores, preoperative pregabalin use has been associated with decreased post-operative nausea and vomiting.[8-9] Decreased nausea and increased constipation in the setting of medical abortion could potentially decrease the commonly experienced emesis and diarrhea associated with misoprostol use.

Many dosages of pregabalin have been studied for analgesia in acute pain events, from 50 mg to 600 mg, with single dose and multiple dose regimens used. Using the Dixon sequential up-down method with participants receiving intradermal capsaicin injections as a marker of acute pain, the dose of pregabalin needed to decrease acute pain by 30% was found to be 252 mg.[11] Based on the suggestion of a dose-effect gradient, limited by an increase in side effects with multiple dosing, we chose to study one 300 mg capsule of pregabalin to maximize benefit without incurring additional side effects. At a cost of approximately six dollars per capsule without insurance coverage, this could be a cost effective adjunct to standard care.

Our primary objective was to evaluate whether prophylactic pregabalin, when co-administered with misoprostol during a medical abortion, reduces maximum pain scores. We also hypothesized that pregabalin would decrease the use of adjuvant narcotic pain medication. As misoprostol is often associated with nausea, vomiting, and diarrhea, pregabalin was also hypothesized to decrease these side effects.

CHAPTER 2: MATERIALS AND METHODS

This was a randomized, double-blind, placebo-controlled trial at the two offices of the University of Hawaii Women's Options Center in Honolulu, Hawaii. The study was approved by the University of Hawaii's Institutional Review Board Committee on Human Studies and registered on clinicaltrials.gov: NCT02782169. After consenting to a medical abortion with their provider, women were approached by a member of the research staff with information about the study. If desired, they provided informed consent for participation. All participants took mifepristone 200 mg orally in the office and were dispensed misoprostol 800 mcg to take buccally at home 24-48 hours later.

Eligibility criteria included age 18 years or older, pregnancy up to and including 70 days gestation by ultrasound dating, and capability and willingness to receive cellular phone text messages and complete multiple electronic surveys over the 72-hour study period. Exclusion criteria included a contraindication or allergy to ibuprofen, oxycodone, acetaminophen, or pregabalin, current use of a gabapentinoid, alternative misoprostol use (i.e. vaginal administration or use in less than 24 hours), inability to speak or read English, or participation in this trial during a prior pregnancy.

Participants were randomized after study consent to one capsule of pregabalin 300 mg or placebo to be swallowed immediately prior to buccal placement of misoprostol. The pregabalin capsules were over-encapsulated by a research pharmacist at the Daniel K. Inouye College of Pharmacy at the University of Hawaii at Hilo. An identical capsule with the same weighted excipient was created as a placebo to maintain blinding. An investigator not involved in recruitment or patient care created a randomization scheme of varied block sizes (4, 6, and 8),

stratified by location for the two offices used for recruitment, using Sealed Envelope Ltd. random sequence generator technology.[12]

The computer-generated randomization list was kept in possession of a second investigator not involved in the care of trial participants, who placed the allocated study capsule in sequentially numbered bags identified only by study identification number. The ordered bags, each containing one capsule of pregabalin or placebo as assigned, were then sent to each study location for distribution as participants were enrolled. The randomization scheme was kept secure from all study personnel and care providers for the duration of the study. No interim analysis was performed and all data was collected prior to un-blinding. In case of severe adverse events, the second investigator holding the randomization scheme would be able to identify and report whether the participant had received pregabalin or placebo.

A supply of twelve ibuprofen 800 mg tablets and eight oxycodone and acetaminophen 5/325 mg tablets were dispensed to all participants for analgesia to be taken as needed. Ibuprofen was advised for first line use, one tablet (800 mg) every six hours as needed, not to exceed four tablets (3200 mg) in 24 hours. Oxycodone with acetaminophen was advised to use for breakthrough pain after ibuprofen, one tablet (5/325 mg) every three to four hours as needed. Baseline demographic information was collected, including age, race, education level, past medical history, medications, gestational age by ultrasound in days, past pregnancy history, and anticipated maximum pain from the upcoming abortion on an 11-point numerical rating scale (NRS).

Data was collected over the 72-hour study period through six online surveys at specified time points. Participants were asked to complete the first survey immediately after taking the study medication capsule and misoprostol. The link to that first survey was provided at the time

of enrollment via SMS text to the participants' cellular phone, and was also printed on the bag containing the study capsule. The survey included an 11-point NRS pain scale, the type and number of analgesic tablets taken since mifepristone administration in the office, and a checklist of potential side effects including a free text field.

After completion of the first survey, an SMS text prompt was sent automatically after 2-, 6-, 12-, 24-, and 72-hours. Each prompt included a link to a new survey that contained the same questions as the first as well as a measure of maximal pain by NRS since the previous survey. This data point allowed us to collect maximum pain points that may have been missed by the real time surveys. At 24-hours post-study medication and misoprostol, a 5-point Likert scale assessed satisfaction with the abortion process and analgesia regimen. At 72-hours, maximum pain scores were collected for both days since the previous survey. See Appendix A for a copy of each survey.

If participants did not provide survey responses, they were contacted by text (after two and six hours without response), phone (after 24 hours), and e-mail (after 72 hours) to provide a retrospective report. Participants were remunerated for each response, with a bonus for completion of all six surveys. All text message prompts and phone calls were sent from a locked cellular phone dedicated to the research trial, held by an investigator at all times. The automated SMS prompts were scheduled through the Android application "SMS Scheduler."

The primary outcome was maximum pain score on the 11-point NRS. The trial was powered to detect a clinically significant reduction in pain with pregabalin of 1.3 on the 11-point NRS.[13-14] Based on a trial by Raymond et al using the same dosage of mifepristone, buccal misoprostol, ibuprofen with breakthrough narcotic for analgesia, and NRS pain scales, we anticipated the maximum pain score in the placebo group to be 7.3 ± 2.2.[2] Assuming a normal

distribution, a sample size of 92 (46 in each arm) would have 80% power to detect a difference in mean pain score of 1.3 with a significance level of 0.05 using a two-sided t-test. If found to not follow a normal distribution, a sample size of 84 (42 in each arm) would have the same power using a two-sided Mann-Whitney U test. To account for up to a 20% drop-out rate using this new method of data collection (text message link to multiple online surveys), we aimed to enroll 110 participants.

We followed an intention-to-treat analysis, including all participants who provided a response for maximum pain, either in real time surveys or in retrospective report. Categorical variables were analyzed using Chi square and Fisher exact tests. Continuous variables were analyzed with t-tests and Mann-Whitney U tests. Analysis was performed using the Statistical Package for Social Sciences (SPSS) software version 24.

CHAPTER 3: RESULTS

From June 2015 to October 2016, a total of 241 women presenting for medical abortion at the Women's Options Centers were screened for inclusion in the trial, with 110 participants enrolled and randomized (Figure 1). The most common reasons for exclusion were desire for alternative routes of misoprostol administration (n=22) or allergy or contraindication to ibuprofen, acetaminophen, or oxycodone (n=14). Three women were excluded because they lacked access to a cellular phone or internet, and four women were excluded because they had already participated in this trial during a prior pregnancy.

Three participants were lost to follow-up after randomization, did not provide any survey responses, and were excluded from the analysis. One participant in each group did not take the study capsule as directed, but were analyzed according to their assigned group. There were no reported severe adverse events, and no un-blinding occurred during the trial.

Baseline demographic characteristics were similar between groups (Table 1). The mean age of participants was 27 years (range 18-41), with a mean gestational age of 54 days (range 41-70). Most women self-identified as Asian, White, or Native Hawaiian, and over one-third identified with more than one race. Seventy-seven percent received some education after high school. Nineteen percent had a history of depression, and 15% had a history of anxiety. This was the first pregnancy for 30% of the participants; 58% were parous, and 45% had a previous abortion (37% surgical, 12% medical, and 4% with a history of both).

Over 93% of women in the trial completed all six surveys (Table 2). The majority of surveys were completed within two hours of the scheduled time (77%) (Table 3). When surveys

were returned late (18%), retrospective maximum pain scores were provided. Four percent of the surveys were never returned.

Blinding was well maintained, with 59.3% of the pregabalin group correctly identifying that they received pregabalin. In the placebo group, 40.8% correctly identified that they received a placebo. Fifty nine percent of both groups believed that they received pregabalin (p=0.99).

After enrollment and data collection was completed, pain scores were found to follow a normal distribution, so pain score analysis was performed using means and t-tests. Participants in both groups had a mean anticipated maximum pain score of 6.75 (standard deviations 1.97 for pregabalin and 2.04 for placebo; p=0.99) (Table 4). The experienced mean maximum pain scores were 5.0 ± 2.6 and 5.5 ± 2.2 in the pregabalin and placebo groups, respectively (p=0.32). The ranked pain scores were also not statistically different between study groups (p=0.64) (Figure 2).

Actual pain scores were lower than expected for 69% of the pregabalin group and 56% of the placebo group (p=0.16). Thirty-five percent of participants anticipated severe range pain (NRS 8-10), but only 14.5% of the pregabalin group and 17% of the placebo group experienced pain of that level (p=0.70). Five percent of women thought that they would experience only mild range pain (NRS 0-3), but 27% of the pregabalin group and 13.5% of the placebo group reported a maximum of mild pain (p=0.08). The majority (64%) of participants had a maximum of moderate range pain (NRS 4-7).

When pain scores in the pregabalin group were compared to the placebo group by weeks of gestation, women at 7-8 weeks gestation reported lower maximum pain scores with pregabalin over placebo (4.9 ± 2.5 versus 6.6 ± 2.0; p=0.04). At 9-10 weeks, maximum pain scores with pregabalin were lower as well (3.9 ± 1.6 versus 5.3 ± 2.2), however, the number of participants

in this cohort were too small to detect a significant difference, if one exists (n=15). The other gestational age groups did not differ significantly.

Mean pain scores over time are graphically represented in Figure 3. Prior to taking the study capsule, participants in the pregabalin group reported statistically higher pain levels, though both were less than one on the NRS (0.7 ± 1.3 versus 0.3 ± 0.9; p=0.04). Between hours two and six, maximum pain scores were lower in the pregabalin group (3.6 ± 2.5 versus 4.6 ± 2.3; p=0.04), with the same finding between hours six and twelve (1.9 ± 2.2 versus 2.8 ± 2.0; p=0.04). No other time points differed statistically between groups. From hour 12 on, 62-80% of participants who received pregabalin reported no pain at each time point. For the placebo group, 46-82% reported no pain in the same period. Means hovered around one on the NRS starting at 12 hours until the end of the study period (0.5-1.2 pregabalin, 0.2-1.1 placebo).

The number of analgesic tablets taken was not normally distributed, and was analyzed by nonparametric tests. Median ibuprofen use was one tablet in the pregabalin group and two tablets in the placebo group (p=0.34) (Table 5). Both groups had a range of 0-8 tablets. Median oxycodone with acetaminophen use was 0 tablets in the pregabalin group and 0.5 tablets in the placebo group (p=0.11) (Table 6). Those that received pregabalin used 0-5 tablets of oxycodone with acetaminophen, and the placebo group used 0-8 tablets. Analgesic use prior to taking the study capsule did not differ between groups, with 30.9% in the pregabalin group taking ibuprofen versus 19.2% in the placebo group (p=0.17), and 7.3% versus 3.8% taking oxycodone with acetaminophen (p=0.68).

Pregabalin use was associated with not requiring any additional analgesics. No ibuprofen was ever used during the abortion for 27.3% in the pregabalin group compared to 11.5% in the placebo group (p=0.04). Those taking pregabalin were also more likely not to take any

oxycodone with acetaminophen: 69.1% compared to 50% (p=0.04). To further understand the potential analgesic-sparing effect of pregabalin, only analgesics taken after the misoprostol and study capsule were considered. Excluding from analysis women who took ibuprofen prior to the study capsule, no ibuprofen was ever taken by 39.5% in the pregabalin group and 14.3% in the placebo group (p=0.01). Excluding prophylactic oxycodone with acetaminophen users from the analysis, 74.5% in the pregabalin group never required a narcotic compared to 52% in the placebo group (p<0.02).

The side effect profiles of each group are shown in Table 7. Participants who received pregabalin reported significantly less constipation than placebo (p<0.02), but significantly more dizziness (p<0.001). When including only side effects reported after taking the study capsule, dizziness was more significant in the pregabalin group (p<0.0001), as was sleepiness (p<0.04) and blurred vision (p<0.05), while no difference remained for constipation. There was no difference between groups for nausea, vomiting, diarrhea, headache, or dry mouth.

Graphic representations of side effects over time are represented in Figure 4. For pregabalin, the percentage of participants reporting sleepiness and dizziness peaked in the first 6 hours, and then fell to lower than placebo by 24 hours for the duration of the study. Blurred vision similarly peaked for pregabalin in the first 6 hours, coming down to 0% by 24 hours.

Satisfaction scores are shown in Table 8. In the pregabalin group, 40.7% were very satisfied with the abortion process, compared with 21.6% in the placebo group (p=0.03). Satisfaction with analgesia was also higher in the pregabalin group, with 47.2% very satisfied with their pain control compared to 21.6% in the placebo group (p=0.006).

CHAPTER 4: DISCUSSION

Although this trial did not find a difference between groups in maximum mean pain scores, pregabalin was associated with higher satisfaction scores and a greater likelihood of not needing any additional analgesics. In the pregabalin group, 27% of women taking pregabalin never took ibuprofen, and up to 40% if excluding the users who took ibuprofen prophylactically. This result compares to 12% and 14% in the placebo group, respectively ($p=0.04$ and $p=0.01$). The same is seen with oxycodone with acetaminophen, with 69-75% never using a narcotic in the pregabalin group, compared to 50-52% in the placebo group ($p=0.04$ and $p<0.02$). This finding is in contrast to previous reports of narcotic use in up to 75% of medical abortion patients.[5] Given the potential for substance use disorders and side effects of narcotics, decreasing the need for narcotic analgesia could have substantial public health benefit. This trial also provides evidence that if narcotics are prescribed to patients for a medical abortion, a very small number of pills should be initially dispensed.

Maximum pain scores were lower than expected, with a mean maximum of 5.5 in the placebo group compared to 7-8 as seen in previous research.[2-4] Many studies have used different mifepristone doses, routes and dosages of misoprostol, and analgesic regimens, though the trial on which the power calculation was based used the same medical abortion regimen and timing as this study.[2] One potential reason for lower reported pain scores is the real time and short interval data collection tool. This allowed for immediate recording of pain scores, not relying on retrospective report and potential recall bias.

Pain duration was shorter than expected based on previous research, with over half of participants in both groups being pain free by 12 hours after misoprostol. This is in contrast to a

previous study where 60% of participants using the same medical abortion regimen reported pain lasting five or more days.[2] That study did not report how much pain was present each day, so it is possible that the mean pain score was similar to the score of less than one on the NRS that was seen here.

Reported pain scores were also lower than the participants had expected, 1.3-1.8 points lower on the NRS than they anticipated at enrollment for placebo and pregabalin, respectively. Previous studies have shown pain during a medical abortion to be less than expected in 30-40% of cases.[2,15] In this study, 56% of the placebo group found the pain to be less than expected, compared to 69% in the pregabalin group (p=0.16). This could partially be due to a placebo effect, since participants knew they were enrolling in a pain management study. Over half of participants in each group believed they received the active study medication, which may have also influenced their perception of pain.

Side effects were high in both groups, particularly gastrointestinal side effects, which are commonly experienced in early pregnancy as well as following misoprostol. Over 80% of women in the placebo group reported nausea at least once during the study period, almost 60% vomiting, and over 50% diarrhea. These numbers were less in the pregabalin group, but not significantly. Notably, rates of nausea were highest (60%) prior to taking the misoprostol, possibly representing the high baseline rate of nausea in a pregnant population.

Pregabalin was associated with higher rates of sleepiness, dizziness, and blurred vision, which are all known side effects of pregabalin. Each of these side effects peaked at six hours, coming down below the rate of the placebo group by 24 hours (or to 0% in the case of blurred vision). Despite the increase in sleepiness, dizziness, and blurred vision, the pregabalin group still had higher satisfaction scores with the abortion (very satisfied: 41% versus 22%; p=0.03)

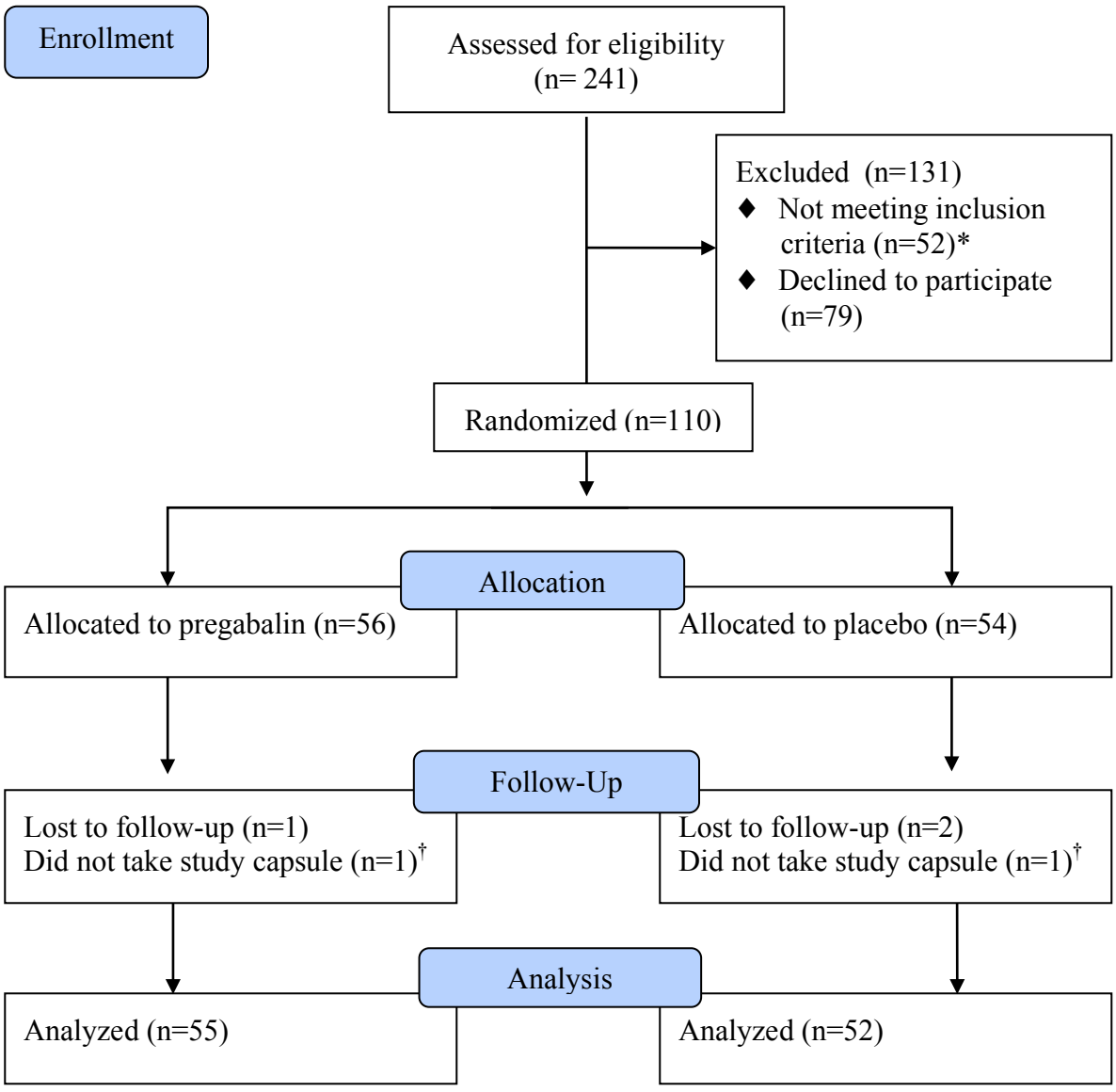
and their pain control (very satisfied: 47% versus 22%; p=0.006). This cannot be attributed to inadequate blinding, as equal numbers of participants in each group believed they received the pregabalin (59%; p=0.99).

Strengths of this study include the randomized, double-blinded, controlled trial design and the high follow-up with 93.6% of participants completing all six surveys and only 2.7% lost to follow-up. Our combination of text message prompt and online survey data collection tool may have contributed to this success. A study by Lim et al showed online diaries to be preferred by study participants (51%) as well as most complete, when compared to SMS or paper diaries.[16] Other studies have also shown SMS acceptability, feasibility, and up to a 100% response rate.[17-18] The prompt via SMS allowed participants immediate access to the survey, while protecting their privacy by redirecting them to a site where only an identification code was required without use of any personal identifiers. Only three women (1.2% of those assessed for eligibility) were excluded due to lack of cellular phone or internet access.

One limitation of this study is that it only included the buccal route of misoprostol administration. We specifically included only women taking buccal misoprostol at least 24 hours after mifepristone in order to standardize the regimen to what the majority of our patients choose and to model the study after the trial on which we based our power calculation.[2] Other routes of misoprostol administration (oral, vaginal, and sublingual) have shown differing side effect profiles, pain scores, and have different timing options for administration after mifepristone.[19] This single regimen may limit generalizability to other modes of misoprostol administration, though there is no reason to believe that the mechanism of action for pregabalin as an analgesic would be altered. The racial diversity of this trial may also limit its generalizability, with over half of participants identifying as Asian and over 30% identifying as Native Hawaiian.

All pain studies are limited by the subjective nature of pain reporting. We chose to use multiple data points and real-time assessments to improve validity and mitigate recall bias. When studying pain, it may be that a maximum pain score is not the most important outcome. A peak value at a moment in time may not truly represent a longitudinal experience. Future research may look to other markers, such as pain over time as measured by area under the curve. Perhaps surrogate markers such as satisfaction or need for analgesics are more important than a peak value as well. While peak pain scores were not decreased with pregabalin, its association with increased satisfaction and decreased need for NSAIDs and narcotics along with its ease of administration may make it a worthwhile adjunct and deserving of further study.

Figure 1: Study flow



*Exclusions: Alternative misoprostol regimen (i.e. vaginal or rapid interval) (n=22), allergy to analgesia regimen (n=14), age <18 years (n=5), non-English speaking (n=4), prior participation in the trial (n=4), no access to cellular phone or internet (n=3).
† Analysis included the two participants who did not take the study capsule as directed.

Table 1: Baseline characteristics of participants

Demographics	Pregabalin (n=55)	Placebo (n=52)	P-value
Age			
Mean (years)	27.25±5.45	27.19±6.02	0.96
Race †			
White	20 (36.4%)	21 (40.4%)	0.67
Black	4 (7.3%)	3 (5.8%)	1.00*
Asian	34 (61.8%)	27 (51.9%)	0.30
Native Hawaiian	17 (30.9%)	17 (32.7%)	0.84
Hispanic	10 (18.2%)	7 (13.5%)	0.50
Other	4 (7.3%)	3 (5.8%)	1.00*
Multiracial	23 (41.8%)	21 (40.4%)	0.88
Education			0.10
Some high school	0 (0%)	3 (5.8%)	
Graduated high school	8 (14.5%)	13 (25%)	
Some college	29 (52.7%)	24 (46.2%)	
Graduated college	15 (27.3%)	12 (23.1%)	
Post-college degree	3 (5.5%)	0 (0%)	
Mental Health			
Depression	11 (20%)	10 (19.2%)	0.92
Anxiety	7 (12.7%)	9 (17.3%)	0.51
Pregnancy history			
First pregnancy	16 (29.1%)	16 (30.8%)	0.85
Prior surgical abortion	22 (40%)	18 (34.6%)	0.57
Prior medical abortion	6 (10.9%)	7 (13.5%)	0.69
Prior miscarriage	13 (23.6%)	11 (22.2%)	0.76
Parous	33 (60%)	29 (55.8%)	0.66
Prior vaginal delivery	29 (52.7%)	25 (48.1%)	0.63
Prior cesarean section	5 (9.1%)	7 (13.5%)	0.47
Gestational age			
Mean (days)	53.51±8.16	55.15±6.90	0.26
Groups (days)			0.62
41-49	19 (34.5%)	14 (26.9%)	
50-56	14 (25.5%)	19 (36.5%)	
57-63	15 (27.3%)	12 (23.1%)	
64-70	7 (12.7%)	7 (13.5%)	

Data are n (%) or mean ± standard deviation.
Categorical variables were compared with Chi square or Fisher exact tests (*), and continuous variables were compared with t-tests.
† Participants could select more than one race.

Table 2: Survey response rate

Number of surveys received	Pregabalin (n=56)	Placebo (n=54)	Total (n=110)
0/6	1 (1.8%)	2 (3.7%)	3 (2.7%)
1/6	0 (0%)	1 (1.9%)	1 (0.9%)
2/6	0 (0%)	0 (0%)	0 (0%)
3/6	0 (0%)	0 (0%)	0 (0%)
4/6	0 (0%)	1 (1.9%)	1 (0.9%)
5/6	1 (1.8%)	1 (1.9%)	2 (1.8%)
6/6	54 (96.4%)	49 (90.7%)	103 (93.6%)

Data are n (%).

Table 3: Survey response time

Surveys received (each row n=110)	On Time	>2 Hours Late	Never submitted
0 hours	94 (85.5%)	12 (10.9%)	4 (3.6%)
2 hours	90 (81.8%)	15 (13.6%)	5 (4.5%)
6 hours	82 (74.5%)	23 (20.9%)	5 (4.5%)
12 hours	72 (65.5%)	34 (30.9%)	4 (3.6%)
24 hours	90 (81.8%)	17 (15.5%)	3 (2.7%)
72 hours	83 (75.5%)	21 (19.1%)	6 (5.5%)

Data are n (%).

Table 4: Pain scores

Pain scores (on NRS 0-10)	Pregabalin (n=55)	Placebo (n=52)	P-value
Anticipated maximum pain score			
Mean	6.75±1.97	6.75±2.04	0.99
Severity			0.64
Mild (0-3)	2 (3.6%)	4 (7.7%)	
Moderate (4-7)	33 (60%)	31 (59.6%)	
Severe (8-10)	20 (36.4%)	17 (32.7%)	
Experienced maximum pain score			
Mean	5.00±2.62	5.46±2.17	0.32
Severity			0.21
Mild (0-3)	15 (27.3%)	7 (13.5%)	
Moderate (4-7)	32 (58.2%)	36 (69.2%)	
Severe (8-10)	8 (14.5%)	9 (17.3%)	
By gestational age			
41-49 days	5.26±2.77	4.64±1.78	0.47
50-56 days	4.93±2.53	6.63±2.03	0.04
57-63 days	5.27±2.96	4.67±2.19	0.56
64-70 days	3.86±1.57	5.29±2.21	0.19
Experienced pain compared to anticipated pain			0.18
More than expected	14 (25.5%)	15 (28.9%)	
Same as expected	3 (5.5%)	8 (15.4%)	
Less than expected	38 (69.1%)	29 (55.8%)	
Pain scores (mean)			
Baseline (0 hours)	0.69±1.29	0.25±0.85	0.04
0-2 hour maximum	3.52±2.76	3.14±2.51	0.47
At 2 hours	2.62±1.93	3.06±1.99	0.25
2-6 hour maximum	3.58±2.53	4.56±2.31	0.04
At 6 hours	2.29±2.18	2.66±1.87	0.35
6-12 hour maximum	1.90±2.17	2.76±1.96	0.04
At 12 hours	0.85±1.65	0.76±1.23	0.75
12-24 hour maximum	0.89±1.80	1.10±1.33	0.50
At 24 hours	0.51±1.51	0.38±0.84	0.60
24-48 hour maximum	0.93±1.88	1.12±1.78	0.59
48-72 hour maximum	1.19±2.19	0.94±1.63	0.52
At 72 hours	0.46±1.50	0.22±0.51	0.27

NRS = numerical rating scale
Data are n (%) or mean ± standard deviation.
Categorical variables were compared with Chi square or Fisher exact tests (*), and continuous variables were compared with t-tests.

Figure 2: Distribution of maximum pain scores

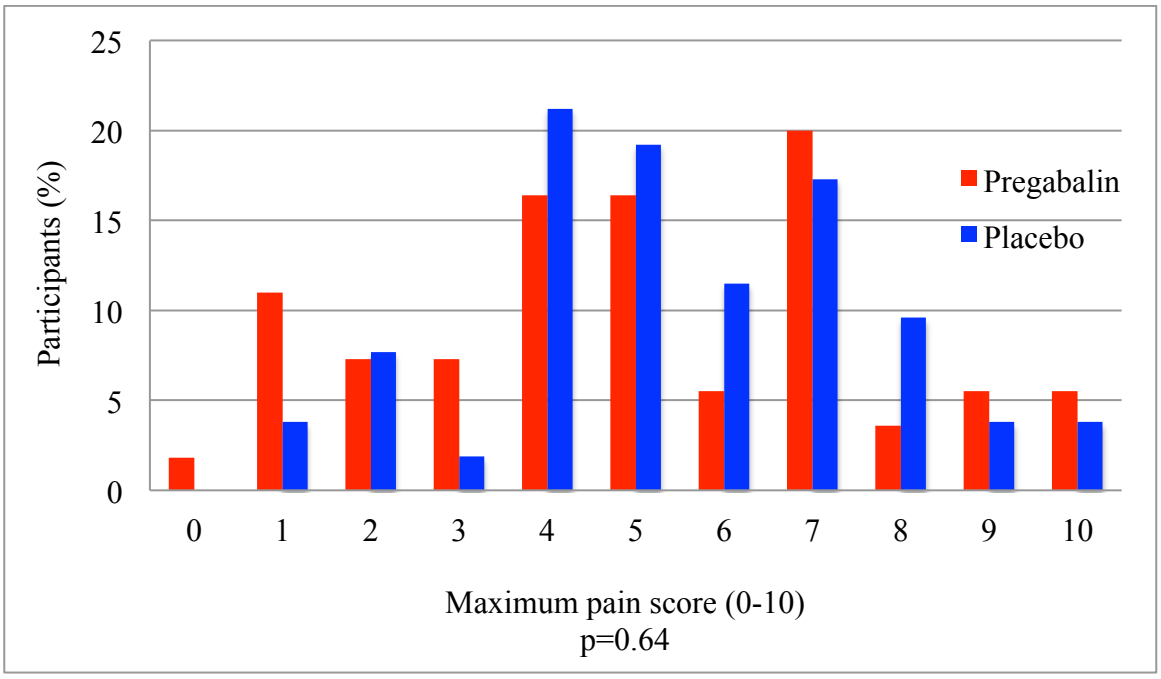
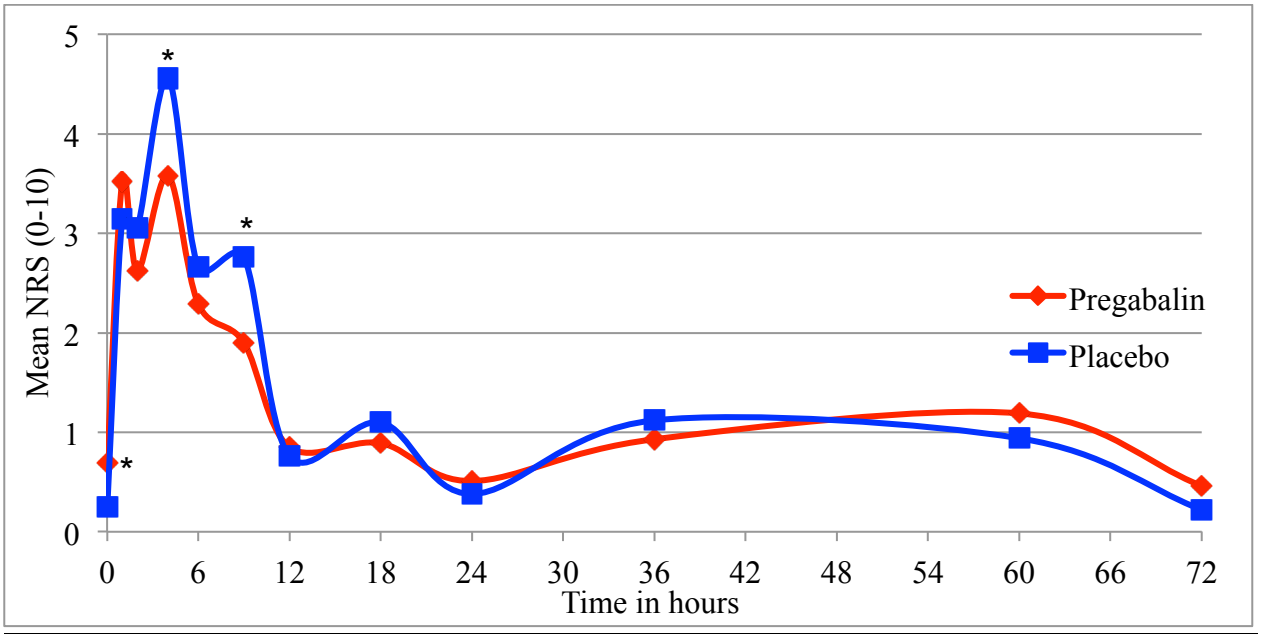


Figure 3: Pain scores over time



* p=0.04 at time points 0, 4, and 9 hours.

Table 5: Ibuprofen use

Ibuprofen 800 mg tablets	Pregabalin (n=55)	Placebo (n=52)	P-value
Prophylactic use	17 (30.9%)	10 (19.2%)	0.17
Total tablets (including prophylactic)			
Median	1 (0-4)	2 (1-3)	0.34
Ever use	40 (72.7%)	46 (88.5%)	0.04
Number used			0.06
0	15 (27.3%)	6 (11.5%)	
1	13 (23.6%)	16 (30.8%)	
2	11 (20%)	10 (19.2%)	
3	2 (3.6%)	11 (21.2%)	
4	5 (9.1%)	5 (9.6%)	
5	3 (5.5%)	2 (3.8%)	
6	3 (5.5%)	1 (1.9%)	
7	2 (3.6%)	0 (0%)	
8	1 (1.8%)	1 (1.9%)	
Total tablets (excluding prophylactic users)	(n=38)	(n=42)	
Median	1 (0-2)	1.5 (1-3)	0.06
Ever use	23 (60.5%)	36 (85.7%)	0.01
Number used			0.15
0	15 (39.5%)	6 (14.3%)	
1	9 (23.7%)	15 (35.7%)	
2	7 (18.4%)	9 (21.4%)	
3	1 (2.6%)	5 (12.5%)	
4	4 (10.5%)	2 (5%)	
5	1 (2.6%)	2 (5%)	
6	1 (2.6%)	1 (2.5%)	
7	0 (0%)	0 (0%)	
8	0 (0%)	1 (2.5%)	

Data are n (%) or median (interquartile range).
Categorical variables were compared with the Chi square test, and continuous variables were compared with Mann-Whitney U tests.

Table 6: Oxycodone with acetaminophen use

Oxycodone with acetaminophen 5/325 mg tablet use	Pregabalin (n=55)	Placebo (n=52)	P-value
Prophylactic use	4 (7.3%)	2 (3.8%)	0.68*
Total tablets (including prophylactic)			
Median	0 (0-1)	0.5 (0-1)	0.11
Ever use	17 (30.9%)	26 (50%)	0.04
Number used			0.07
0	38 (69.1%)	26 (50%)	
1	7 (12.7%)	14 (26.9%)	
2	3 (5.5%)	7 (13.5%)	
3	1 (1.8%)	2 (3.8%)	
4	5 (9.1%)	1 (1.9%)	
5	1 (1.8%)	1 (1.9%)	
6	0 (0%)	0 (0%)	
7	0 (0%)	0 (0%)	
8	0 (0%)	1 (1.9%)	
Total tablets (excluding prophylactic users)	(n=51)	(n=50)	
Median	0 (0-1)	0 (0-1)	0.03
Ever use	13 (25.5%)	24 (48%)	<0.02
Number used			0.05
0	38 (74.5%)	26 (52%)	
1	6 (11.8%)	14 (28%)	
2	2 (3.9%)	7 (14%)	
3	0 (0%)	1 (2%)	
4	4 (7.8%)	1 (2%)	
5	1 (2%)	1 (2%)	

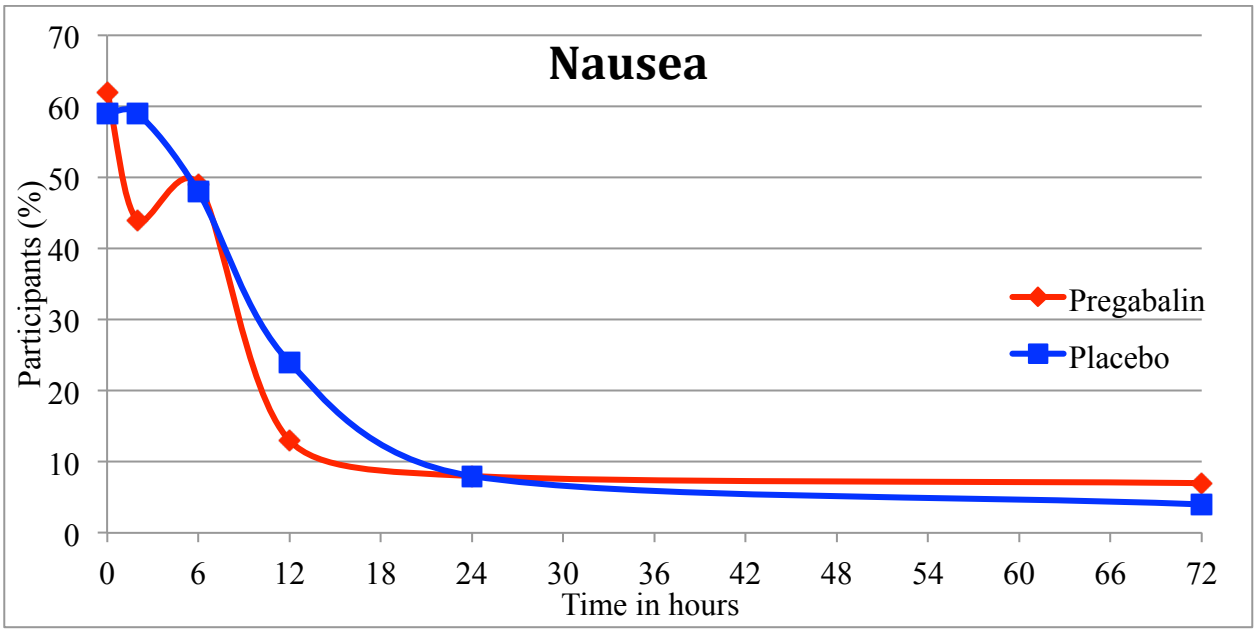
Data are n (%) or median (interquartile range).
Categorical variables were compared with Chi square or Fisher exact tests (*) and continuous variables were compared with Mann-Whitney U tests.

Table 7: Side effects

Side effects	Pregabalin (n=55)	Placebo (n=52)	P-value
Ever			
Nausea	43 (78.2%)	42 (80.8%)	0.74
Vomiting	28 (50.9%)	30 (58.8%)	0.41
Sleepiness	47 (85.5%)	39 (76.5%)	0.24
Dizziness	45 (81.8%)	26 (50%)	<0.001
Headache	28 (50.9%)	17 (33.3%)	0.07
Blurred vision	15 (27.3%)	7 (13.7%)	0.09
Diarrhea	28 (50.9%)	29 (56.9%)	0.54
Constipation	6 (10.9%)	15 (29.4%)	<0.02
Dry mouth	22 (40%)	25 (48.1%)	0.40
After study capsule			
Nausea	37 (67.3%)	38 (73.1%)	0.51
Vomiting	20 (36.4%)	25 (49%)	0.19
Sleepy	47 (85.5%)	35 (68.6%)	<0.04
Dizzy	45 (81.8%)	22 (42.3%)	<0.0001
Headache	17 (30.9%)	15 (29.4%)	0.87
Blurred vision	15 (27.3%)	6 (11.8%)	<0.05
Diarrhea	25 (45.5%)	28 (54.9%)	0.33
Constipation	5 (9.1%)	11 (21.6%)	0.07
Dry mouth	21 (38.2%)	21 (40.4%)	0.82

Data are n (%).

Figure 4: Side effects over time



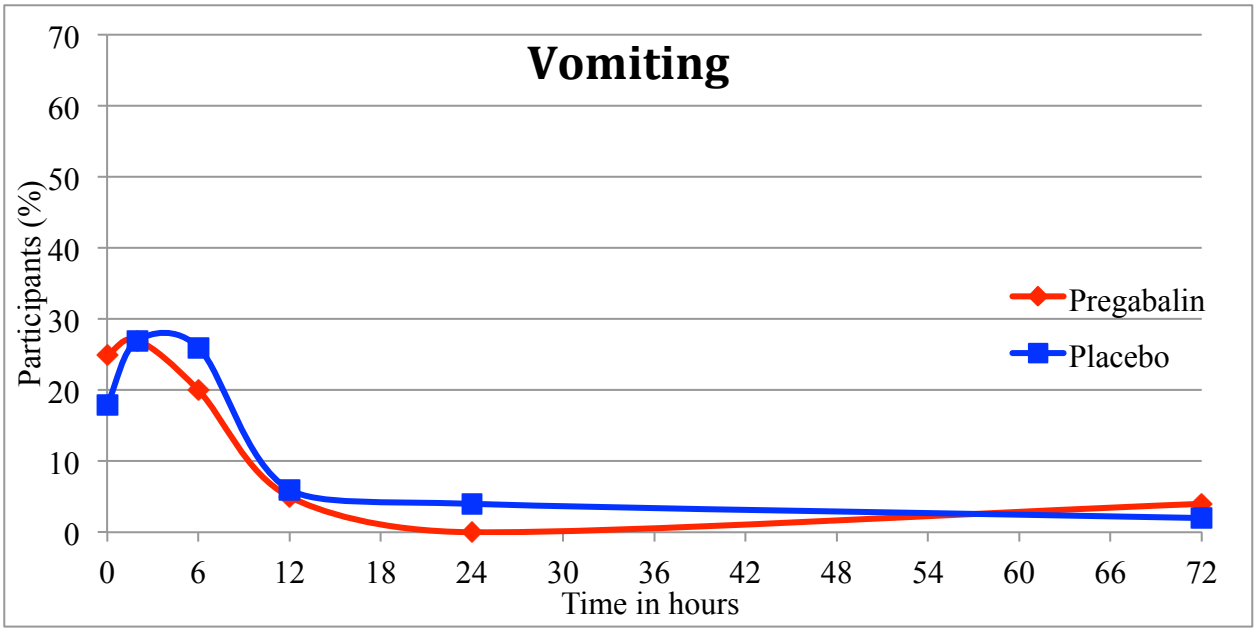
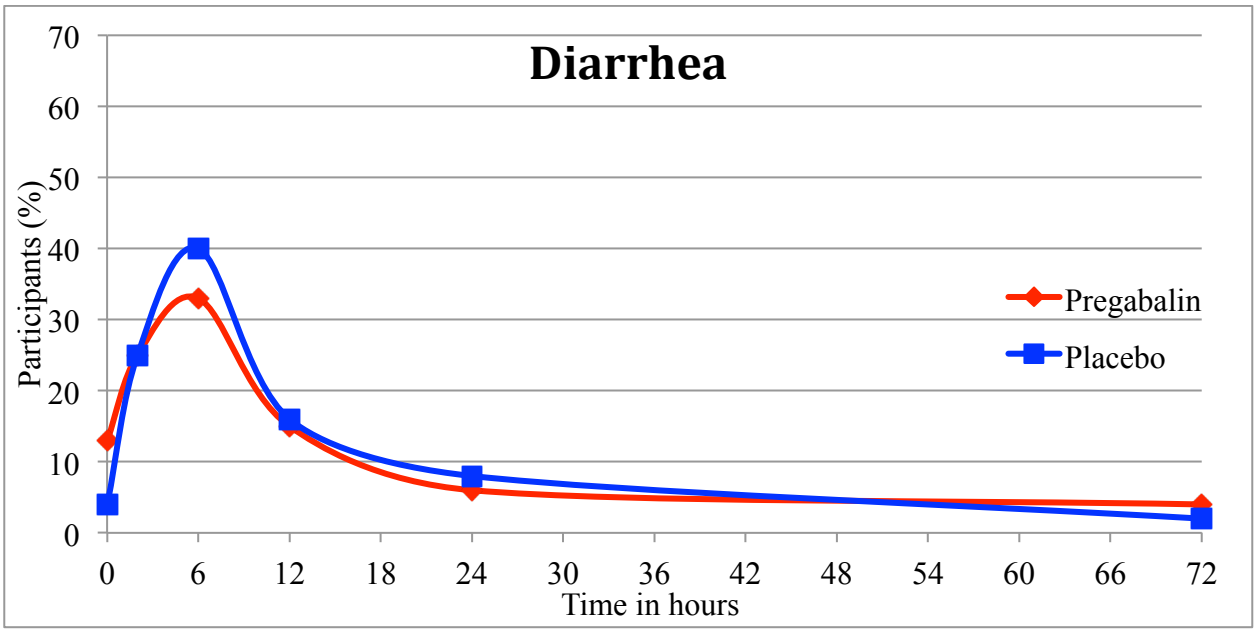


Figure 4 (Continued): Side effects over time



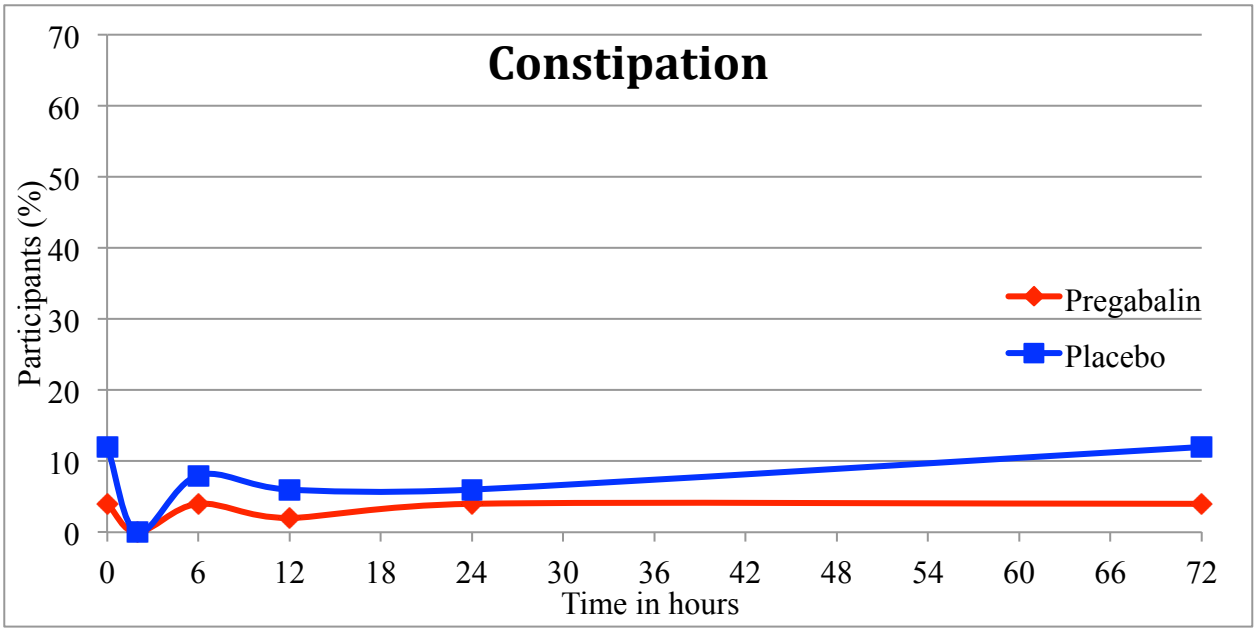
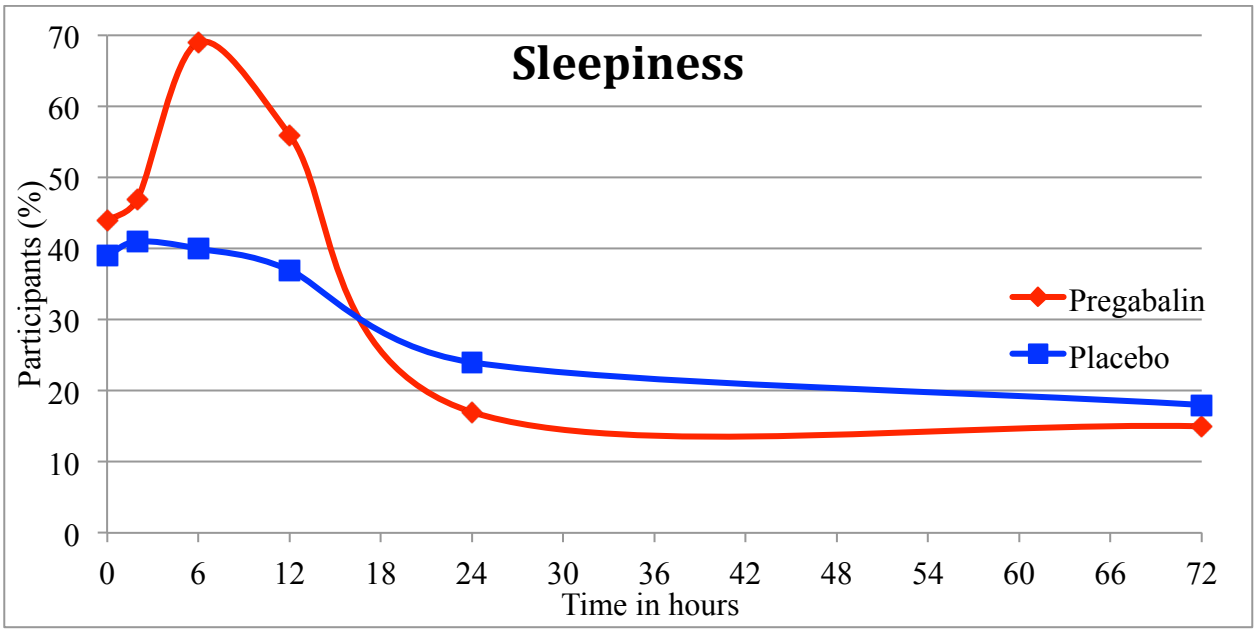


Figure 4 (Continued): Side effects over time



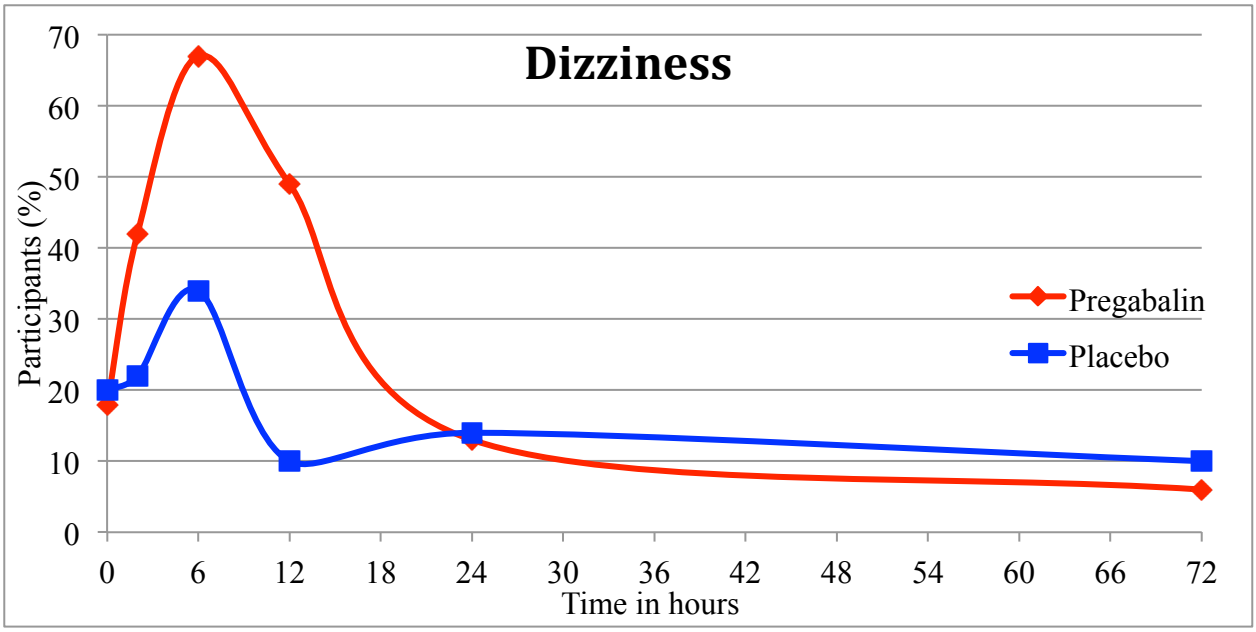
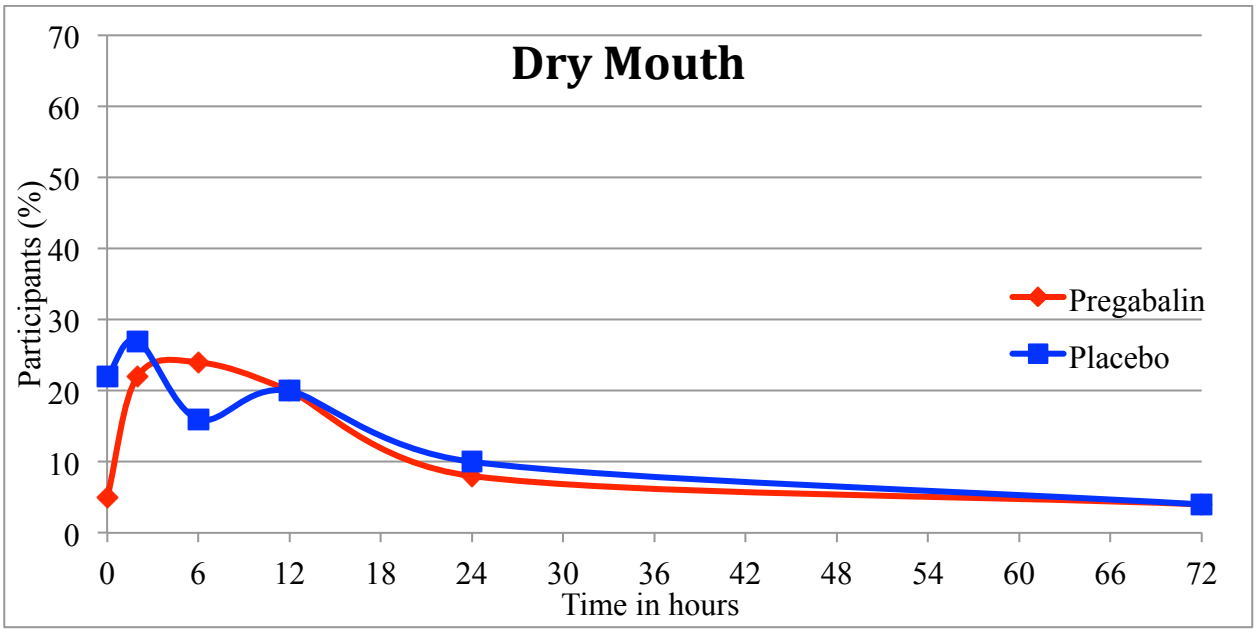


Figure 4 (Continued): Side effects over time



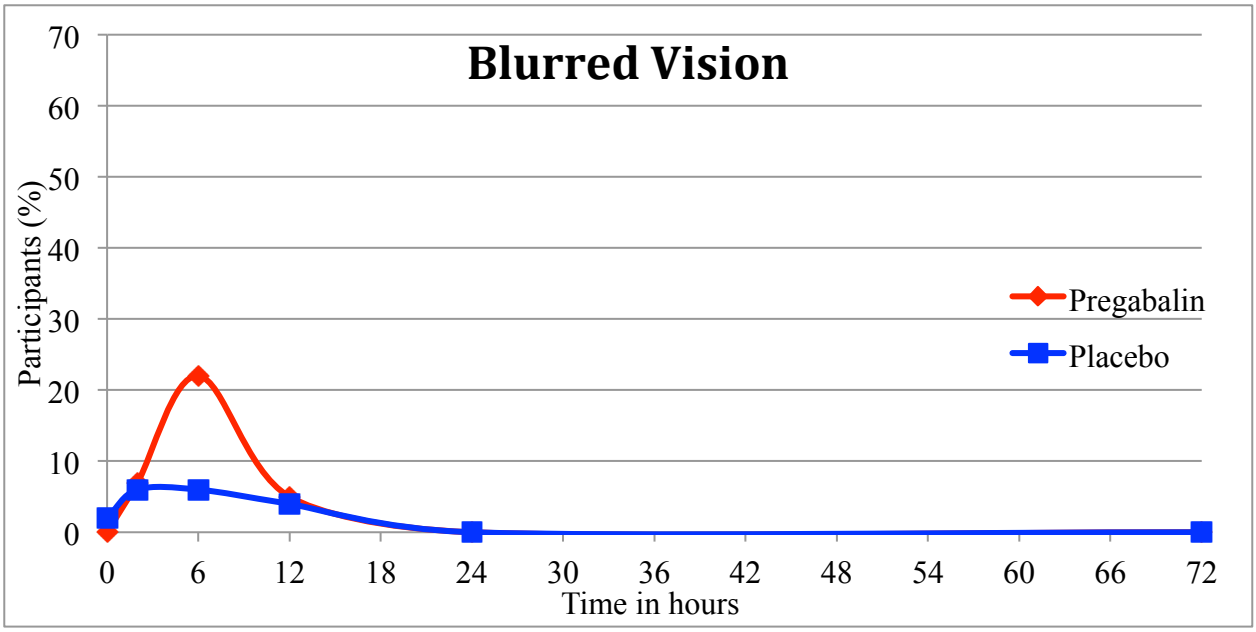


Table 8: Satisfaction scores

Likert scale 1-5	Pregabalin	Placebo	P-value
Abortion satisfaction	(n=54)	(n=51)	0.18
Very dissatisfied	1 (1.9%)	0 (0%)	
Dissatisfied	1 (1.9%)	2 (3.9%)	
Neutral	12 (22.2%)	18 (35.3%)	
Satisfied	18 (33.3%)	20 (39.2%)	
Very satisfied	22 (40.7%)	11 (21.6%)	0.003*
Analgesia satisfaction	(n=53)	(n=51)	0.009
Very dissatisfied	2 (3.8%)	3 (5.9%)	
Dissatisfied	3 (5.7%)	0 (0%)	
Neutral	12 (22.6%)	13 (25.5%)	
Satisfied	11 (20.8%)	24 (47.1%)	
Very satisfied	25 (47.2%)	11 (21.6%)	0.006*

Data are n (%).

* P-value represents "very satisfied" compared to all other responses.

APPENDIX A – STUDY SURVEYS

Baseline survey (hour 0):

Pain Study - Baseline - Hour 0

Please make sure you take the misoprostol tablets as well as the study medication capsule before taking this survey

What is your study ID number?

(located on your pill packet)

What is the word you chose at your study visit?

(any word that you can remember and will use when submitting all of your surveys, to help identify your responses without using your name)

Did you take the misoprostol tablets?

- ☐ Yes, just now.
- ☐ Yes (please enter time under "other" below)
- ☐ No (please specify why under "other" below)
- ☐ Other:

Did you take the study medication capsule (pregabalin or placebo)?

- ☐ Yes, just now.
- ☐ Yes (please enter time under "other" below)
- ☐ No (please specify why under "other" below)
- ☐ Other:

What is your pain level right now?

	0	1	2	3	4	5	6	7	8	9	10	
No pain	○	○	○	○	○	○	○	○	○	○	○	Most pain

What was your highest level of pain since the office visit?

(not including your current pain level)

	0	1	2	3	4	5	6	7	8	9	10	
No pain	○	○	○	○	○	○	○	○	○	○	○	Most pain

When was your highest pain level since the office visit?

(Be as specific as you can, for example: 1 hour ago, or 10:30am. You can estimate, or if unsure, write "unsure" or "can't remember")

How many tablets of ibuprofen 800mg have you taken since the office visit?

- ○ 0
- ○ 1
- ○ Other:

How many tablets of oxycodone/acetaminophen 5/325mg have you taken since the office visit?

- ○ 0
- ○ 1
- ○ Other:

Did you have any of the following symptoms since your office visit?

Select all that apply

- ☐ 1 = nausea
- ☐ 2 = vomiting
- ☐ 3 = sleepy
- ☐ 4 = dizzy
- ☐ 5 = headache
- ☐ 6 = blurred vision
- ☐ 7 = diarrhea
- ☐ 8 = constipation
- ☐ 9 = dry mouth
- ☐ 10 = none of the above
- ☐ Other:

Submit

Survey #2 (2 hours):

Pain Study - Hour 2

2 hours after taking medication

What is your study ID number?
(located on your pill packet)

What is the word you chose at your study visit?
(any word that you can remember and will use when submitting all of your surveys, to help identify your responses without using your name)

What is your pain level right now?

	0	1	2	3	4	5	6	7	8	9	10	
No pain	○	○	○	○	○	○	○	○	○	○	○	Most pain

What was your highest level of pain since the last survey?
(not including your current pain level)

	0	1	2	3	4	5	6	7	8	9	10	
No pain	○	○	○	○	○	○	○	○	○	○	○	Most pain

When was your highest pain level since the last survey?
(Be as specific as you can, for example: 1 hour ago, or 10:30am. You can estimate, or if unsure, write "unsure" or "can't remember")

How many tablets of ibuprofen 800mg have you taken since the last survey?

- ○ 0
- ○ 1
- ○ Other:

How many tablets of oxycodone/acetaminophen 5/325mg have you taken since the last survey?

- ○ 0
- ○ 1
- ○ Other:

Did you have any of the following symptoms since the last survey?

Select all that apply

- ☐ 1 = nausea
- ☐ 2 = vomiting
- ☐ 3 = sleepy
- ☐ 4 = dizzy
- ☐ 5 = headache
- ☐ 6 = blurred vision
- ☐ 7 = diarrhea
- ☐ 8 = constipation
- ☐ 9 = dry mouth
- ☐ 10 = none of the above
- ☐ Other:

Submit

Surveys #3 (6 hours) and #4 (12 hours) with identical questions to survey #2, only with different time points.

Survey #5 (24 hours):

Pain Study - Hour 24

24 hours after taking medication

What is your study ID number?
(located on your pill packet)

What is the word you chose at your study visit?
(any word that you can remember and will use when submitting all of your surveys, to help identify your responses without using your name)

What is your pain level right now?

	0	1	2	3	4	5	6	7	8	9	10	
No pain	○	○	○	○	○	○	○	○	○	○	○	Most pain

What was your highest level of pain since the last survey?
(12 hours ago)

	0	1	2	3	4	5	6	7	8	9	10	
No pain	○	○	○	○	○	○	○	○	○	○	○	Most pain

When was your highest pain level since the last survey?
(Be as specific as you can, for example: 1 hour ago, or 10:30am. You can estimate, or if unsure, write "unsure" or "can't remember")

How many tablets of ibuprofen 800mg have you taken since the last survey?

- ○ 0
- ○ 1
- ○ 2
- ○ 3
- ○ 4
- ○ Other:

How many tablets of oxycodone/acetaminophen 5/325mg have you taken since the last survey?

- ○ 0
- ○ 1
- ○ 2
- ○ 3
- ○ 4
- ○ Other:

Did you have any of the following symptoms since the last survey?

Select all that apply

- ☐ 1 = nausea
- ☐ 2 = vomiting
- ☐ 3 = sleepy
- ☐ 4 = dizzy
- ☐ 5 = headache
- ☐ 6 = blurred vision
- ☐ 7 = diarrhea
- ☐ 8 = constipation
- ☐ 9 = dry mouth
- ☐ 10 = none of the above
- ☐ Other:

What was your satisfaction level with the abortion process overall?

- ○ 1 = very dissatisfied
- ○ 2 = dissatisfied
- ○ 3 = neutral
- ○ 4 = satisfied
- ○ 5 = very satisfied

What was your satisfaction level with your pain control?

- ○ 1 = very dissatisfied
- ○ 2 = dissatisfied
- ○ 3 = neutral
- ○ 4 = satisfied
- ○ 5 = very satisfied

Do you think you took the study medication or the placebo?

- ○ 1 = study medication
- ○ 2 = placebo

Submit

Survey #6 (72 hours):

Pain Study - Hour 72

72 hours after taking medication

What is your study ID number?
(located on your pill packet)

What is the word you chose at your study visit?
(any word that you can remember and will use when submitting all of your surveys, to help identify your responses without using your name)

What is your pain level right now?

	0	1	2	3	4	5	6	7	8	9	10	
No pain	○	○	○	○	○	○	○	○	○	○	○	Most pain

What was your highest level of pain in the 24 hours following the last survey?
(2 days ago)

	0	1	2	3	4	5	6	7	8	9	10	
No pain	○	○	○	○	○	○	○	○	○	○	○	Most pain

When was your highest pain level in that 24 hour period?
(Be as specific as you can, for example: 10:30am. You can estimate by time of day, or if unsure, write "unsure" or "can't remember")

What was your highest level of pain in the last 24 hours?

	0	1	2	3	4	5	6	7	8	9	10	
No pain	○	○	○	○	○	○	○	○	○	○	○	Most pain

When was your highest pain level in the last 24 hours?

(Be as specific as you can, for example: 10:30am. You can estimate by time of day, or if unsure, write "unsure" or "can't remember")

How many tablets of ibuprofen 800mg have you taken since the last survey?

- ○ 0
- ○ 1
- ○ 2
- ○ 3
- ○ 4
- ○ Other:

How many tablets of oxycodone/acetaminophen 5/325mg have you taken since the last survey?

- ○ 0
- ○ 1
- ○ 2
- ○ 3
- ○ 4
- ○ Other:

Did you have any of the following symptoms since the last survey?

Select all that apply

- ☐ 1 = nausea
- ☐ 2 = vomiting
- ☐ 3 = sleepy
- ☐ 4 = dizzy
- ☐ 5 = headache
- ☐ 6 = blurred vision
- ☐ 7 = diarrhea
- ☐ 8 = constipation
- ☐ 9 = dry mouth
- ☐ 10 = none of the above
- ☐ Other:

What was your highest level of pain during the whole process?

	0	1	2	3	4	5	6	7	8	9	10	
No pain	○	○	○	○	○	○	○	○	○	○	○	Most pain

When was your highest level of pain?

(Be as specific as you can, for example: "1 hour after taking the study medication," or "the first 6 hours," or "the whole second day." You can estimate, or if unsure, write "unsure" or "can't remember")

Submit

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